Definition, identification and treatment of resistant hypertension in chronic kidney disease patients

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ABSTRACT

Resistant hypertension, the inability to achieve goal blood pressure despite the use of three or more appropriately dosed antihypertensive drugs (including a diuretic), remains a common clinical problem, especially in patients with chronic kidney disease (CKD). While the exact prevalence and prognosis of resistant hypertension in CKD patients remain unknown, resistant hypertension likely contributes significantly to increased cardiovascular risk and progression of kidney disease in this population. We review the identification and evaluation of patients with resistant hypertension, including the importance of 24-h ambulatory blood pressure monitoring in the identification of ‘white-coat’, ‘masked’ and ‘non-dipper’ hypertension, the latter of which has particular clinical and therapeutic importance in patients with resistant hypertension and CKD. We then discuss treatment strategies for resistant hypertension that target the pathophysiologic mechanisms underlying resistance to treatment, including persistent volume excess, incomplete renin-angiotensin-aldosterone system blockade and inadequate nocturnal blood pressure control. Finally, we propose a treatment algorithm for evaluation and treatment of resistant hypertension in patients with CKD.

Keywords: algorithm, chronic kidney disease, resistant hypertension

INTRODUCTION

Resistant hypertension is defined as blood pressure (BP) that remains above goal despite adherence to treatment with at least three antihypertensive agents prescribed at optimal doses, ideally including a diuretic [1]. By this definition, patients with resistant hypertension include those who are able to achieve BP control but require four or more antihypertensive medications at full doses to do so. While somewhat arbitrary in terms of the number of medications required, this definition helps identify those patients who are at highest risk for the adverse outcomes associated with persistently elevated blood pressure and who may benefit most from therapy.

The prevalence of resistant hypertension is unknown, in part due to the feasibility of conducting a large, forced titration study to answer this question appropriately. However, data from the National Health and Nutrition Examination Survey (NHANES) from 2003 to 2008 suggest that 12.8% of the antihypertensive-treated population meets the criteria for resistant hypertension [2]; this number may rise to >50% in nephrology clinics [3]. Indeed, in the first study to specifically address this question in 300 hypertensive chronic kidney disease (CKD) patients referred to a nephrology clinic, 38% met the definition of resistant hypertension after 6 months of blood pressure management, with a higher prevalence of diabetic nephropathy and higher levels of proteinuria emerging among the patients with resistant hypertension [4]. A number of factors may contribute to the pathogenesis and higher prevalence of resistant hypertension in CKD, including impaired sodium handling, increased activity of the renin-angiotensin-aldosterone (RAAS) and sympathetic systems, impaired nitric oxide synthesis and endothelium-mediated vasodilation, and increased arterial stiffness [5–8]. The relationship between these factors has important implications for the identification and treatment of resistant hypertension in CKD (non-end stage renal disease) patients, the topic of this review.

DEFINITION

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood
Pressure (JNC 7), published in 2003, identifies a treatment goal of <140/90 mm Hg for patients with hypertension and no other compelling conditions, and includes a separate recommendation for a goal BP of <130/80 mm Hg for all patients with CKD, defined as either reduced glomerular filtration rate (GFR) or the presence of albuminuria (>300 mg/day or 200 mg/g creatinine) [9]. Likewise, a number of guidelines recommend a lower target blood pressure for patients with hypertension who are at high risk for cardiovascular disease, which includes those with CKD [10, 11].

Data supporting a goal of <130/80 to slow progression of CKD or to reduce cardiovascular disease risk in CKD are not robust. Indeed, the greatest benefit of targeting a blood pressure of <130/80 has been demonstrated in patients with advanced, proteinuric CKD and stems from two large trials of patients with predominantly non-diabetic CKD and mean GFR <60 mL/min/1.73 m², the Modification of Diet in Renal Disease Study (MDRD) and the African American Study of Kidney Disease (AASK) [12, 13]. In the primary analysis of both studies, randomization to a low blood pressure group (mean arterial pressure <92 mm Hg, equivalent to BP <125/75) versus the usual blood pressure group (mean arterial pressure <107 mm Hg, equivalent to BP <140/90) did not result in slowing progression of CKD at 3 years in MDRD and at 4 years in AASK [12, 13]. However, in subgroup analysis, both studies revealed trends favoring lower BP goals in patients with higher baseline proteinuria. As we await updates in the JNC and other guidelines, the most conservative approach is to classify proteinuric CKD patients with BP >130/80 and non-proteinuric CKD patients with BP >140/90 as above goal.

**IDENTIFICATION**

In the evaluation and treatment of patients with apparent resistant hypertension, ‘pseudo-resistant’ hypertension, or the appearance of treatment resistance, must first be distinguished from true resistant hypertension. Factors that can contribute to elevated blood pressure readings in a patient who does not truly have resistant hypertension include improper blood pressure measurement technique, difficult to compress heavily calcified or atherosclerotic arteries in the elderly, poor adherence to prescribed treatment and the phenomenon of ‘white-coat’ hypertension [14]. Poor adherence to therapy is a common cause of apparent treatment resistance. Retrospective cohort studies suggest that ~40% of patients with newly diagnosed hypertension will discontinue treatment during the first year, and only 40% will continue with therapy during the first 5 or 10 years of follow-up [15–17]. Poor adherence to treatment can be identified through the use of self-report tools, pharmacy refill rates and pill counts. A number of methods can be used to improve adherence, including selection of medications with low side effect profiles, simplification of the medication regimen through once daily dosing and use of fixed-dose combinations, and improved communication between patients and physicians regarding patient knowledge, awareness, beliefs and attitudes [18]. Given the high rates of treatment discontinuation, interventions to enhance medication adherence therefore have the potential to overcome a significant component of apparent treatment resistance.

Two additional causes of pseudo-resistance are related to the antihypertensive regimen itself: (i) suboptimal dosing of medications or inappropriate combinations of agents and (ii) clinician inertia, a failure to change or increase dose regimens in order to obtain adequate treatment of poorly controlled hypertension despite awareness of the condition. Studies conducted among primary care physicians suggest that many physicians have higher BP thresholds for initiation and modification of drug therapy than the recommended treatment goals, and many are not familiar with the JNC guidelines [19]. Perhaps a greater understanding of what determines physicians’ thresholds for making treatment decisions, and education regarding treatment guidelines and available medical decision algorithms, can improve adherence to evidence-based recommendations and attainment of treatment goals.

Confirmation of true resistant hypertension should include the accurate measurement of office blood pressure, with attention to environment, body and arm position, appropriate cuffs, and the recommendation that multiple measurements be obtained at least 1 min apart and averaged out [20]. Nonetheless, office blood pressure measurement has shortcomings, and the use of out-of-office monitoring including home and 24-h ambulatory blood pressure monitoring (ABPM) is becoming increasingly important. ABPM, which involves readings taken at preset intervals throughout the day and night to capture the diurnal rhythm and variability of blood pressure over 24 h, can help detect ‘white-coat’ hypertension, an elevation in blood pressure that occurs during clinic visits, with normal blood pressure in non-clinic settings and absence of target organ damage [21]. The confirmation of white-coat hypertension, a common cause of pseudo-resistance, identifies patients who are relatively low risk and therefore unlikely to benefit from additional antihypertensive therapy. In one study of patients with apparent resistant hypertension, 28% were found to have normal awake ambulatory blood pressure when ABPM was used to complement office BP measurements [22].

Twenty-four-hour ABPM has, in fact, been shown to be the best method for estimating a patient’s hypertension-related cardiovascular risk [23]. ABPM can identify patients with ‘masked’ hypertension, which is defined as elevated ambulatory blood pressure but normal clinic blood pressure, and has been associated with an increased risk of cardiovascular events. In a study of 466 patients with apparent responder hypertension based on clinic measurements, ambulatory BP monitoring found 27% to have ‘masked’ hypertension, which over a follow-up period of 5 years was associated with a relative risk of 2.28 (95% CI, 1.1–4.7; P < 0.05) of fatal and nonfatal cardiovascular events, compared with true responder hypertension [24].

Moreover, ABPM provides clinicians with the ability to capture nighttime blood pressures and to identify the presence of a ‘non-dipping’ pattern, which is the diminution or reversal of the normal 10–20% nocturnal fall in blood pressure that occurs in both normotensive and hypertensive individuals. Nighttime blood pressure is a potent predictor of cardiovascular risk, and in a cohort study of 7458 patients,
nighttime BP was found to be a stronger predictor than daytime blood pressure of total and cardiovascular mortality [25]. Similarly, non-dipping has been shown to confer an ∼2-fold greater risk of cardiovascular mortality compared with a normal dipping pattern, independent of the presence of hypertension (i.e. even with a normal 24-h blood pressure) [26]. In a study of 556 patients with resistant hypertension, a non-dipping pattern was present in 65% and was an independent predictor of the composite end point of fatal or nonfatal cardiovascular events, all-cause mortality and cardiovascular mortality (hazard ratio, 1.74; 95% CI, 1.12–2.71) [27].

ABPM takes on greater importance in the CKD population with hypertension, as both non-dipping and masked hypertension are more common among patients with CKD. In the AASK Cohort Study, a remarkable 80% of the participants were non-dippers, and of the 377 participants with controlled clinic BP, 70% had masked hypertension [28]. Higher night-time BP and masked hypertension were associated with increased severity of target organ damage, including higher prevalence of left ventricular hypertrophy (LVH) and proteinuria and lower estimated GFR. Accordingly, in a large cohort of 436 hypertensive patients with CKD, ABPM has been shown to be a better predictor of renal and cardiovascular end points compared with office BP measurements, with nighttime systolic BP emerging as a stronger predictor than daytime systolic BP among the components of ABPM [29]. As this study suggests, the prognostic role of ABPM is superior to that of office BP among CKD patients. However, ABPM is associated with increased time, effort and expense, and prospective studies that randomize CKD patients to therapeutic interventions based on ABPM rather than office BP are required before ABPM can be recommended as standard of care in all CKD patients [30].

In addition to the above considerations, a number of factors can impair control of preexisting hypertension and contribute to the development of resistance, particularly in CKD patients. Renal artery stenosis, most commonly caused by atherosclerosis, has a reported prevalence in the Medicare population of 0.5% overall but 5.5% in those with CKD [31]. Moreover, as this represents symptomatic renovascular disease, and renal artery stenosis is usually asymptomatic, the true disease burden is likely higher. While the frequency of resistant hypertension resulting from renovascular disease is unknown, hypertension and symptomatic disease of the extra-renal vasculature are strongly associated with prevalent renovascular disease, and hemodynamically significant renal artery stenosis may contribute to treatment resistance [32]. Increased arterial stiffness is a common finding in patients with CKD and has also been associated with resistant hypertension [33]. Increased arterial stiffness in CKD may be a consequence of a number of pathologic mechanisms, including vascular calcification, chronic volume overload, inflammation, endothelial dysfunction, oxidative stress and activation of the RAAS, and has been shown to progress in a stepwise manner across the stages of CKD [34, 35]. This association carries important consequences for both identification and treatment of resistant hypertension, as arterial stiffness has been associated with increased cardiovascular morbidity and mortality in both hypertension and in CKD [34, 36].

Obesity is another common co-morbidity seen in both resistant hypertension and CKD, and may mediate hypertension through a number of mechanisms including impaired sodium excretion, enhanced sympathetic nervous system activity, increased aldosterone secretion due to visceral adiposity and obstructive sleep apnea (OSA) [14]. Severe OSA, in particular, has been linked to resistant hypertension in patients with advanced CKD, though an independent association between severe OSA and resistant hypertension has thus far only been demonstrated in dialysis patients [37].

**TREATMENT**

The approach to treatment of resistant hypertension in patients with CKD should aim to address the multitude of factors that contribute to the pathogenesis of hypertension in this population, including impaired handling of sodium and volume expansion, increased activity of the renin-angiotensin-aldosterone system, enhanced sympathetic activity and reduced endothelium-dependent vasodilation. Particular focus should be lent to patterns of elevated blood pressure that have been found to be more prevalent in this population and to increase the risk of target organ damage, including elevated nighttime BP and the presence of non-dipping.

**Volume**

Salt restriction has been shown to lower blood pressure in patients with and without hypertension. In the Dietary Approaches to Stop Hypertension (DASH)-Sodium trial, sodium reduction from 150 to 100 mmol per day generally had twice the effect on blood pressure as reduction from 150 to 100 mmol per day [38]. The effect of dietary sodium restriction on the degree of BP reduction appears to be particularly robust in patients with resistant hypertension. In a small, randomized crossover trial of patients with resistant hypertension, a low (50 mmol/ day) compared with high (250 mmol/day) sodium diet decreased mean office systolic BP (SBP) by 22.7 mm Hg and led to significant reductions in daytime, nighttime and 24-h ambulatory blood pressure [39].

Thus, patients with resistant hypertension, as well as those with CKD, demonstrate particularly salt-sensitive hypertension. Patients with CKD have an impaired ability to effectively excrete sodium and will respond to a sodium load by raising blood pressure in order to re-establish salt balance; this ‘pressure natriuresis’ comes at the expense of hypertension-related target organ damage [8]. In addition, dietary sodium intake has been shown to interact with the RAAS, particularly aldosterone, in both animal models and human studies, to mediate hypertension, vascular and tissue damage and kidney disease [40]. In a study of patients with resistant hypertension and high 24-h urinary aldosterone, urinary protein excretion increased significantly with progressively greater salt intake, suggesting that aldosterone excess and high dietary sodium intake interact to increase proteinuria [41]. Indeed, in a randomized, double-blind,
placebo-controlled crossover study in proteinuric patients without diabetes, salt restriction itself exerted an antihypertensive and antiproteinuric effect and further enhanced the antiproteinuric effects of RAAS blockade to nearly the same magnitude as, and in an additive manner with, diuretics [42]. While this study and others have demonstrated the beneficial impact of sodium restriction on intermediate renal outcomes in CKD, it is important to note that no large cohort studies have shown sodium restriction to reduce BP or long-term cardiovascular and overall mortality specifically in CKD patients [43]. Therefore, the recommendation for sodium restriction in the treatment of hypertension in CKD and in the reduction of cardiovascular and overall mortality in CKD patients remains largely opinion-based.

The salt-excreting handicap of CKD and resulting extracellular volume expansion also provides the basis for treating hypertensive CKD patients with diuretics. Studies of resistant hypertension suggest that, even in the absence of CKD, this group of patients manifest increased extracellular volume, as measured by brain-type natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) [44]. Therefore, use of appropriate diuretics is a cornerstone of therapy in patients with CKD and resistant hypertension [9]. Nonetheless, diuretics remain underutilized and underdosed, and a change in diuretic therapy may help a significant proportion of patients with resistant hypertension achieve BP goals [14]. For example, while the major trials supporting the use of diuretic therapy used chlorthalidone at 25 mg/day, the weaker hydrochlorothiazide (HCTZ) at doses of 12.5–25 mg/day remains the most commonly prescribed antihypertensive medication worldwide [45]. However, when evaluated with 24-h ambulatory BP monitoring, the antihypertensive efficacy of HCTZ at doses of 12.5–25 mg/day has been shown to be inferior to that of other commonly prescribed drug classes [45]. Chlorthalidone is approximately twice as potent as HCTZ with a much longer duration of action (8–15 h for HCTZ compared with >40 h for chlorthalidone) [46]. In clinical studies using 24-h ABPM, chlorthalidone 25 mg/day results in greater reductions in 24-h mean SBP compared with HCTZ 50 mg/day, primarily due to its effect on reducing nighttime mean SBP [47]. Therefore, strong consideration should be given to using chlorthalidone over HCTZ, especially given the growing importance of nocturnal blood pressure on cardiovascular outcomes and kidney disease progression in patients with CKD.

Thiazide diuretics are most effective in patients with a GFR >50 mL/min/1.73 m², although chlorthalidone can be effective to a GFR of 30–40 mL/min/1.73 m² in the absence of severe hypoalbuminemia [14]. A loop diuretic is preferred for patients with advanced CKD. Typically, loop diuretics such as furosemide and bumetanide should be dosed at least twice daily given their short duration of action and the potential for intermittent natriuresis leading to a reactive increase in the RAAS (with ensuing sodium retention) if dosed once daily [48]. The longer-acting torsemide can be dosed once or twice daily. Consideration should also be given to combining the loop diuretic with a diuretic that acts more distally in the nephron, such as a thiazide or a low-dose potassium-sparing diuretic [49].

**Adequate RAAS blockade**

Targeting the RAAS with angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) is a well-established therapeutic strategy to target hypertension, slow the progression of CKD and reduce morbidity and mortality in heart failure. However, many patients progress despite treatment, and clinical trials of ACE inhibitors and ARBs suggest that after an initial decline, plasma aldosterone levels will increase in 30–40% of patients over the long term, a phenomenon known as ‘aldosterone breakthrough’ [50]. Aldosterone breakthrough has been linked to adverse outcomes such as LVH, impaired exercise capacity, urinary albumin excretion and a more rapid decline in GFR [50]. This breakthrough is particularly important given the recent shift in our understanding of the role of aldosterone in mediating hypertension and target organ damage. Namely, the classical view that aldosterone acts primarily upon epithelial tissues to regulate intravascular volume and sodium and potassium homeostasis has been broadened by the identification of the mineralocorticoid receptor (MR) in non-epithelial tissues including the heart, kidney, vasculature and brain. A number of studies in both animals and humans have demonstrated the widespread effects of aldosterone in mediating vascular damage, inflammation and tissue fibrosis, mainly in the presence of a high-salt environment that potentiates the deleterious effect of MR activation [51].

One therapeutic option to target incomplete blockade of the RAAS is dual blockade with the combination of ACE inhibitors and ARBs, which has been shown to confer modest BP reductions of an average of 4/3 mm Hg compared with monotherapy as well as proteinuria reductions of 30 and 39% compared with monotherapy with ACE inhibitors and ARBs, respectively [52]. However, improved cardiovascular and renal outcomes have not been consistently demonstrated despite these additional reductions in BP and proteinuria. An alternative strategy is to use ‘ultrahigh’ doses of ACE inhibitors or ARBs. Several small, short-term clinical studies in patients with hypertension and CKD have found significant incremental reductions in proteinuria after treatment with ARBs at higher than conventional doses, albeit without additional blood pressure changes [53]. One large, randomized, open-label trial of 360 patients with non-diabetic proteinuric CKD followed for >3 years found that ‘optimal’ antiproteinuric doses of benazepril and losartan, achieved through up titration from conventional doses of 10 mg/day for benazepril and 50 mg/day for losartan, were associated with a 51 (P = 0.03) and 53% (P = 0.02) reduction, respectively, in the combined primary end point of doubling of serum creatinine, end stage renal disease or death [54]. However, optimal antiproteinuric efficacy was obtained in 57% of patients with a losartan dose of 100 mg/day, which would be considered a standard dose. These data suggest that while most patients achieve maximal antihypertensive and antiproteinuric efficacy at conventional doses of ACE inhibitors and ARBs, some patients with hypertension and CKD may require higher doses to achieve a more optimal degree of RAAS blockade. Theoretically, these resistant patients are displaying a form of aldosterone breakthrough.
Hence, suppressing the RAAS with mineralocorticoid receptor blockers (MRBs), such as spironolactone and eplerenone, has gained renewed interest as a treatment for resistant hypertension in patients with and without CKD. While hyperaldosteronism has previously been considered an uncommon cause of resistant hypertension, recent studies have found significantly higher aldosterone levels and an elevated aldosterone to renin ratio (ARR) in over a third of patients with resistant hypertension, despite persistent extracellular volume expansion [44]. In this setting, MRBs have emerged as effective therapy for patients with resistant hypertension, with and without CKD. The strongest evidence for the efficacy of MRBs in resistant hypertension comes from two studies. In 2007, the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) showed that fourth-line add-on therapy with spironolactone, at a median treatment duration of 1.3 years and a starting dose of 25 mg/day, resulted in a mean reduction in SBP of 21.9 mm Hg (95% CI: 20.8–23.0 mm Hg) and in diastolic BP of 9.5 mm Hg (95% CI: 9.0–10.1 mm Hg) [55]. Subsequently, the randomized, double-blind, placebo-controlled Addition of Spironolactone in Patients with Resistant Arterial Hypertension (ASPIRANT) trial demonstrated a mean decrease in daytime systolic ambulatory BP of 5.4 mm Hg (P = 0.02), as well as significant decreases in ABPM nighttime systolic (8.6 mm Hg, P = 0.01), 24-h ABPM systolic (9.8 mm Hg, P = 0.004) and office systolic BP values (6.5 mm Hg, P = 0.01), with spironolactone 25 mg/day at 8 weeks of therapy [56].

The efficacy and safety of MRBs in patients with resistant hypertension who have stages 2 and 3 CKD has been evaluated in several small retrospective studies, which have shown significant and sustained BP reductions with spironolactone and eplerenone at low doses [57, 58]. In a study of 36 patients with mean estimated glomerular filtration rate (eGFR) 48.6 mL/min/1.73 m², the addition of spironolactone at a mean dose 23.6 mg/day or eplerenone at a mean dose 60.4 mg/day resulted in a significant decrease in SBP from 162 ± 22 to 138 ± 14 mm Hg after 1 year of follow-up, and led to discontinuation of at least one antihypertensive medication during follow-up in 44% of patients [57]. These studies have also provided important data on the risk of hyperkalemia in this group of patients. In a cohort of 46 patients with mean eGFR 56.5 ± 16.2 mL/min/1.73 m² who had spironolactone (25 mg/day) or eplerenone (50 mg/day) added to a stable antihypertensive regimen, including a maximally dosed RAAS blocker and an appropriately dosed diuretic, a baseline eGFR ≤ 45 mL/min/1.73 m² and a baseline serum potassium > 4.5 mEq/L were the strongest predictors of hyperkalemia (defined as serum potassium > 5.5 mEq/L) [58]. With close monitoring of potassium, the use of MRBs in patients with early stage CKD, or with later stage CKD and a low baseline potassium level and/or concomitant use of diuretics, can be a safe and effective therapeutic strategy for resistant hypertension.

**Chronotherapy**

Both resistant hypertension and CKD are associated with the phenomenon of non-dipping, an absence of the normal nocturnal decline in BP. In the AASK Cohort Study, 80% of the participants were non-dippers, and those in the highest tertile of nighttime systolic BP were more likely to have LVH, higher prevalence of proteinuria and higher risk of CKD progression [28]. In patients with all degrees of hypertension, particularly true resistant hypertension, the presence of a non-dipping profile has been shown to confer an ~2-fold increased risk of cardiovascular morbidity and mortality [26, 27]. In both resistant hypertension and CKD, a common pathophysiologic mechanism may involve the impaired capacity to excrete sodium during the daytime, leading to higher nocturnal BP and the absence of dipping [59].

In this setting, investigators have evaluated whether chronotherapy—the strategy of bedtime, rather than morning, dosing of antihypertensive medications—can have an impact on the circadian rhythm of BP, including 24-h ambulatory BP control and the prevalence of non-dipping. In a study of 250 patients with resistant hypertension, patients who were randomly assigned to the strategy of changing one drug but administering the new drug at bedtime demonstrated a statistically significant ambulatory blood pressure reduction (9.4/6.0 mm Hg for systolic/diastolic BP, P < 0.001) compared with the strategy of changing one drug but continuing all medications in a single morning dose (Figure 1) [60]. The effect was larger on the nocturnal than on the diurnal mean BP, and the prevalence of non-dipping decreased from 84 to 43% over the 12-week study period. The benefit of chronotherapy has also been demonstrated in resistant hypertension by moving all non-diuretic antihypertensive drugs from morning to bedtime dosing without changing any medications or doses [61]. Thus, chronotherapy offers an opportunity to improve nocturnal BP control and the non-dipper pattern without changing the total number of medications.

![Figure 1: Chronotherapy of hypertension (data from Hermida et al. [60]). Switching blood pressure medications from morning to bedtime dosing can lead to significant improvements in systolic and diastolic blood pressure. This chronotherapy strategy has also recently been shown, in a large study of CKD patients with resistant hypertension, to improve cardiovascular morbidity and mortality.](image-url)
Data regarding chronotherapy in hypertensive patients with CKD are promising. In an uncontrolled, 8-week clinical trial of 32 non-dipper patients with CKD treated with a mean 2.4 antihypertensive medications at baseline, shifting one antihypertensive drug from morning to bedtime dosing restored a ‘dipper’ profile in 87.5% of subjects with significant reductions in systolic and diastolic nocturnal BP [62]. Moreover, urinary protein excretion decreased as well, from 235 ± 250 to 167 ± 206 mg/day (P < 0.001), a change that correlated with the improvement in the night/day BP ratio. Subsequently, in a prospective, randomized, open-label trial of 661 hypertensive patients with CKD, Hermida et al. [63] found that bedtime dosing of at least one antihypertensive medication resulted in significant improvements in nocturnal BP control, attainment of ‘dipper’ status and controlled ambulatory BP, lower adjusted risk of cardiovascular events (adjusted HR, 0.31; 95% CI, 0.21–0.46; P < 0.01) and lower risk for a composite outcome of cardiovascular death, myocardial infarction and stroke (adjusted HR, 0.28; 95% CI, 0.13–0.61; P < 0.001). Bedtime treatment was also associated with a greater percent reduction in albumin excretion from baseline (26.9 versus 15.6% in patients on morning treatment, P = 0.018). The bedtime treatment group also demonstrated slower decline in GFR (0.4 mL/min/1.73 m² versus 2.3 mL/min/1.73 m², P = 0.043), but the absolute differences were small and progression of CKD was not studied as an outcome. Given these data, a reasonable strategy in patients with resistant and/or non-dipping hypertension and CKD is to change one antihypertensive medication to bedtime dosing.

**TREATMENT ALGORITHMS**

Current guidelines recommend initiating treatment with a diuretic, either alone or in combination with an agent that has a different mechanism of action, such as an agent that targets the RAAS. Additional agents with complementary mechanisms of action are then added, in a stepwise fashion, until BP control is achieved [1]. However, limited guidance is provided to clinicians in terms of choice of add-on therapy and individualization of treatment. As a result, as seen in a large general hypertensive cohort, 21% of patients are prescribed ≥3 medications [64].

Several treatment algorithms have been proposed that target the underlying physiology mediating resistance to therapy. In a renin test-guided therapeutic (RTGT) algorithm, ambulatory plasma renin activity (PRA) values obtained from a routine blood sample, regardless of antihypertensive therapy or diet, were used to guide addition and/or subtraction of drugs [65]. Hypertensive patients with low ambulatory PRA (<0.65 ng/mL/h) were presumed to have persistent salt/volume excess that would respond primarily to natriuretic anti-volume (‘V’-type) drugs, including diuretics, aldosterone antagonists, calcium channel blockers or alpha blockers. Patients with PRA ≥0.65 ng/mL/h were considered to have an excess of renin-angiotensin system-related vasoconstrictor activity that would respond to anti-renin (‘R’-type) drugs, including beta blockers, ACE inhibitors or ARBs. For example, in a patient treated with a diuretic and either an ACE inhibitor or ARB, which stimulate renin secretion, a suppressed PRA <0.65 ng/mL/h would suggest stopping or downtitrating the ‘R’ drug and uptitrating or adding a ‘V’ drug. Compared with clinical hypertension specialists’ care (CHSC), RTGT resulted in a 10 mm Hg greater decline in SBP (P = 0.03), generally via subtracting ‘R’ drugs from low-renin patients while adding them to the medium- and high-renin groups and subtracting ‘V’ drugs from high-renin patients while adding them to the other groups. Additional studies have similarly found that baseline PRA can predict the blood pressure response to add-on therapy with beta blockers and thiazide diuretics (higher renin predicting greater BP response to atenolol, and lower renin predicting greater BP response to HCTZ) [66] as well as spironolactone [56], supporting the use of this physiology-based algorithm to provide clues regarding patients’ sodium-volume and/or renin status in order to optimize BP control. In clinical practice, lower PRAs are associated with poorer blood pressure control and use of more antihypertensive medications [64], suggesting that patients with low-renin hypertension can perhaps benefit most from this approach.

Additional algorithms for resistant hypertension also rely on targeting the known physiologic mechanisms mediating hypertension, including salt/volume excess, the RAAS and the sympathetic nervous system (SNS). In patients with resistant hypertension despite a combination regimen directed at both salt/volume excess and the RAAS, the first step would be to identify patients in whom persistent salt/volume excess is sustaining hypertension and who would benefit from bolstering the diuretic regimen [67]. While the presence of edema is an important clinical clue, patients with both resistant hypertension and CKD may manifest occult extracellular volume expansion. As discussed above, suppressed ambulatory PRA, interpreted in the context of existing antihypertensive therapy, can indicate this occult volume excess and need for more diuresis. The second option in this algorithm is the addition of medications directed at SNS-mediated hypertension, mainly α- and β-blockers, in clinical circumstances that suggest hypertension driven by the SNS, such as sleep apnea. In a retrospective study assessing the efficacy of this approach in 27 patients with resistant hypertension, 89% were able to achieve BP control, including 54% in whom the diuretic regimen was strengthened, with the most frequent medication adjustment being the addition of a potassium-sparing diuretic [68].

We propose a screening and treatment algorithm that follows these physiologic approaches to resistant hypertension (Figure 2). Remaining areas of uncertainty that will likely enhance this algorithm include (i) whether to screen for aldosterone breakthrough in all patients treated with RAAS blockade prior to initiating treatment with aldosterone antagonists [50] and (ii) whether chronic therapy should be utilized as a generalized approach or be limited to those patients with resistant hypertension and a 24-h BP profile of non-dipping.

**CONCLUSION**

Despite increased awareness and multiple treatment strategies for hypertension, resistant hypertension remains a
common clinical problem. In the evaluation of patients with apparent resistant hypertension, clinicians should first identify potential causes of pseudo-resistance. Consideration should be given to 24-h ABPM given the gaps in our definition of resistant hypertension, including ‘white-coat’ and ‘masked’ hypertension and the presence of a ‘non-dipping’ pattern, common both in resistant hypertension and in CKD. Treatment should aim to address the many physiologic mechanisms underlying resistant hypertension in this population. We propose a physiology-based algorithm for resistant hypertension in CKD, from identification to treatment, aimed at improving blood pressure control and, ultimately, long-term renal and cardiovascular outcomes.

**CONFLICT OF INTEREST STATEMENT**

None declared.

**REFERENCES**


**FIGURE 2:** A physiology-based algorithm for resistant hypertension in CKD, from identification to treatment.
Ultrafiltration for the treatment of congestion: a window into the lung for a better caress to the heart

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ABSTRACT

A significant proportion of patients treated for acute decompensated heart failure (ADHF) suffer from worsening renal function, which is often associated with medical therapy resistance and poor outcome. In this setting, haemofiltration has been used for more than 30 years, despite inconclusive evidence for its advantages. In the last decade, a major technological advances have made available a new technique, ultrafiltration, which works at lower blood flow rates and requires only a venous access. As in a first proof-of-concept study (EU-PHORIA), ultrafiltration proved to be efficacious in fluid removal in ADHF patients; this treatment was further investigated in randomized controlled trials. The RAPID-CHF trial demonstrated that ultrafiltration was more effective than...